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Has an Observational Study of Early vs Elective Colonoscopy for Acute Lower Gastrointestinal Hemorrhage Answered Questions That Clinical Trials Could Not?

Lisa L. Strate[1] and **Thomas F. Imperiale**[2,3,4]

[1]Division of Gastroenterology, Department of Medicine, Harborview Medical Center, University of Washington Medical School, Seattle, Washington

[2]Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine

[3]Regenstrief Institute, Inc

[4]Center for Innovation, Roudebush VA Medical Center, Indianapolis, Indiana

Colonoscopy is recommended as the initial intervention for most patients presenting with acute lower gastrointestinal bleeding (LGIB).[1] The diagnostic and therapeutic yield of colonoscopy is higher than that of other available interventions including tagged red blood cell scan, CT angiography and angiography, and complications are uncommon.[2] However, there is substantial uncertainty regarding the optimal timing of colonoscopy in the setting of acute LGIB. In a randomized controlled trial (RCT) of 100 patients with acute LGIB, there were significantly more definitive diagnoses made in patients undergoing colonoscopy within 8 hours of initial presentation to the hospital than in patients undergoing elective colonoscopy within 96 hours or tagged red blood scan plus/minus angiography in the presence of ongoing bleeding.[3] Early colonoscopy resulted in more therapeutic interventions and less recurrent bleeding than elective colonoscopy, but these differences were not statistically significant. Another trial randomized 72 patients with LGIB to urgent (within 12 hours of presentation) or delayed (36 to 60 hours after presentation) colonoscopy and found no differences in diagnosis, therapy, or rebleeding rates.[4] The lack of statistically significant differences in these trials may have been a type 2 error due to the small sample sizes. Studies of colonoscopy within 12 hours of presentation in patients with diverticular hemorrhage indicate that major stigmata of recent hemorrhage (i.e., active bleeding, non-bleeding visible vessel and adherent clot) portend a poor prognosis, and that treatment of these stigmata with epinephrine injection and bipolar coagulation or hemoclipping decreases rebleeding and the need for angiography or surgery.[5, 6]

Adding to this slender body of literature is the study by Nagata and colleagues, an observational study of patients with acute LGIB who underwent colonoscopy between January 2009 and December 2014 at the largest hospital in Tokyo, Japan.[7] The study

Corresponding Author: Lisa L. Strate, MD, MPH, Harborview Medical Center, 325 Ninth Avenue; Box 359773, Seattle, WA 98104, (p) 206-744-7058 (f) 206-744-8698.

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objective was to determine the safety and effectiveness of colonoscopy performed early (within 24 hours of presentation) versus electively (beyond 24 hours). Among 176 subject pairs, one of whom had early colonoscopy while the other had elective colonoscopy, there were no differences between the early and elective groups in adverse events, transfusion requirements, or 30-day mortality. The early group was statistically more likely to have major stigmata of recent hemorrhage (26.4% vs 9.2%), to undergo endoscopic therapy (25.8% vs. 8.6%), and to have a shorter hospital length of stay (10.3 vs 13.1 days). Rebleeding within 30 days was more frequent in the early group (13.5% vs 7.4%), but the difference did not reach statistical significance (P=0.07).

The strengths of this study include the large sample size relative to the published trials, its sampling from consecutive cases in a real life setting, clear and clinically-sensible definitions, and comprehensive and systematic use of electronic health data. One study limitation is the exclusion of 94 patients with missing vital signs or no colonoscopy during admission – a limitation that reduced the initial study sample size by 15%, and may have both narrowed the patient spectrum and reduced the potential number of subject pairs. A second limitation is the observational study design, with its risk for bias in how baseline features may affect both the timing of colonoscopy and clinical outcomes.

While RCTs are considered the reference standard for evaluating therapeutic interventions, they are not always feasible. The two published trials on timing of colonoscopy in acute LGIB[3, 4] were limited by inability to accrue a large, representative, and adequately-powered study sample. Observational studies can complement RCTs of therapeutic interventions by quantifying the effects of interventions in real world clinical practice, a setting with broader generalizability and greater clinical heterogeneity than is found in clinical trials. However, the causal link between intervention and outcome is weaker in an observational study because of the potential for biased selection inherent to the study design and for confounding in the analysis.

To equalize the tendency – or propensity – for bleeding severity, comorbidity and other factors to affect the timing of colonoscopy, Nagata and colleagues used a propensity score analysis. A propensity score is the probability of receiving a particular treatment based on baseline features.[8] It is used in an attempt to balance the distribution of these baseline features between 2 or more groups (in the same way that randomization does in a RCT), so that assignment of the intervention in the observational study looks more like that in a clinical trial. While propensity scores may be used analytically in several ways, matching is used most commonly. Matching results in creation of a subgroup of paired subjects – one of whom receives the intervention, the other of whom does not – in which the difference in propensity score is minimized (or at best, is zero). The factors that belong in the score are those that plausibly affect the intervention, and that are unbalanced (statistically or clinically) between the two groups at baseline. In the case of early versus elective colonoscopy for acute LGIB, propensity score variables might include age, comorbidity, endoscopist, anticoagulants, day of the week, and factors that quantify the rate and severity of bleeding. Within the propensity score matched subgroup, these baseline features should be well-balanced, as shown in Table 1 of the Nagata study, which appears similar to Table 1 of a clinical trial comparing baseline features of two or more groups. Outcomes are then

measured within the matched-pairs subgroup. Establishing baseline equivalence between the early and elective groups allows the effect of timing of colonoscopy to be more causally linked to outcomes. How strong the causal link becomes is a function of how well equilibrated the two groups are for baseline features related to colonoscopy timing and whether all of the appropriate baseline features were included.

In addition to reducing selection bias, propensity scores have the statistical advantages of model parsimony and robustness. An alternative to using a propensity score is to include all relevant factors directly in a multivariable logistic regression model. However, when the number of factors relative to outcomes is large, there is a greater risk of creating an overfitted model that may not validate when applied to another patient sample. Propensity scores are a more efficient way to adjust for several factors and also allow for reporting a wider range of measures of effect (i.e., absolute risk and risk reduction, relative risk, number needed to treat), whereas conventional regression is limited to odds and hazard ratios. There are at least two limitations to using a propensity score. One limitation is the inability to adjust for unmeasured factors such as time of presentation and availability of endoscopy support staff. In the Nagata study, how well the propensity score levels the playing field is a function of the degree to which it contains variables related to the timing of colonoscopy. A second limitation is the loss of eligible subjects due to the lack of matched pairs. In the Nagata study, the sample size was reduced from 508 to 326 subjects after matching. Readers interested in learning more about propensity scores are referred to excellent reviews of the topic.[8, 9]

There are several potential explanations for why early colonoscopy in acute lower GI bleeding appears to facilitate the identification and treatment of stigmata of recent hemorrhage, but not decrease rates of rebleeding, surgery and mortality. First, in this study, there were significantly more patients with definitive diverticular and post-polypectomy bleeding in the early vs. elective colonoscopy group. These sources are more likely to result in severe and/or recurrent bleeding than other diagnoses such as colitis, hemorrhoids and NSAID-related ulcers. Alternatively, it is possible that endoscopic hemostasis in the colon is ineffective. Stigmata of recent hemorrhage may tend to resolve spontaneously, and therefore treatment does not improve, and in fact, may worsen outcomes. However, natural history studies of peptic ulcer and diverticular bleeding indicate that SRH are highly predictive of rebleeding in the absence of endoscopic therapy.[6] Therefore, inadequate endoscopic hemostasis is likely to play a role in the disappointing results of the Nagata study and others. The approach to endoscopic hemostasis in the colon has not been standardized, and there is general concern for treatment related complications in the thin-walled colon. Therefore, endoscopists may be less proficient and/or assertive in their approach to hemostasis in the colon than in the upper GI tract. Notably, outcomes in LGIB from specialized GI bleeding centers tend to be more favorable than those from other care settings.[5, 6] Lastly, early colonoscopy could contribute to suboptimal endoscopy conditions such as insufficient hemodynamic resuscitation, and/or colon preparation, and performance of endoscopy outside the endoscopy suite and without trained assistants. In the Nagata study, colon preparation quality was not reported, but there were no differences in the receipt of a full preparation, and definitive diagnoses were more frequent in the early vs. elective colonoscopy group suggesting that poor preparations do not account for the findings.

An important next step in the management of acute LGIB is the identification of effective endoscopic treatment approaches to common colonic bleeding sources, particularly diverticular stigmata. A variety of techniques and their applications are reported, but most have not been systematically studied or compared. Improved methods for risk stratifying patients at the time of presentation are also needed to determine which patients could benefit from early interventions, as existing prediction models do not optimally distinguish high from moderate risk groups. Risk stratification is arguably more important in LGIB than upper GI bleeding given the relative difficulty in performing urgent colonoscopy vs. urgent EGD. Yet, much more is known about high-risk features in upper gastrointestinal bleeding than LGIB. As noted previously, a large, multicenter trial of colonoscopy timing in LGIB would be difficult to orchestrate, and may not be warranted given the available evidence. Even in the setting of UGIB where severe bleeding is relatively common and endoscopic hemostasis is known to improve outcomes, the optimal timing of EGD remains unclear despite extensive investigation. Instead, a systematic review of existing studies of timing of colonoscopy for LGIB, including the Nagata study, would be a logical next step.

In summary, the large, observational, propensity-matched analysis by Nagata and colleagues found that early colonoscopy (within 24 hours of presentation) for acute LGIB was associated with more definitive diagnoses and therapeutic interventions and shorter length of stay, but did not improve transfusion requirements, rebleeding, surgery or mortality. These results corroborate findings from two, small randomized trials. Based on current evidence, colonoscopy next available is appropriate for the majority of patients with acute LGIB. However, more urgent colonoscopy (within 24 hours) may be beneficial in patients with signs and symptoms of severe and/or ongoing bleeding after hemodynamic resuscitation. Future research should focus on improved approaches to endoscopic hemostasis in the colon, and the development of clinical tools for identifying patients at high-risk of adverse outcomes.

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Abbreviations

LGIB	lower gastrointestinal bleeding
NSAID	nonsteroidal anti-inflammatory drug
RCT	randomized controlled trial